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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,057	01/28/2004	Roy H. Larsen	50147/003002	2306

21559 7590 01/21/2010

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EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
01/21/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/766,057	LARSEN ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 25-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 25-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 18 and 25-35 are pending in the application.

Response to Arguments

1. Applicant's arguments filed 10/9/09 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 18 and 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wedeking et al. (US 6,093,382) in view of Sinkule et al. (EP 282057) as stated in the office action mailed 4/9/09.

4. Applicant asserts that Wedeking et al. describes targeting of small molecules (see for example, the molecules described at columns 27 to 32 of Wedeking) using a folate. Even when larger complexes of multiple chelating agents are used and several folates are required in Wedeking et al. (e.g., columns 51 and 52) the molecular weight is fairly low (less than 5000 for the molecule at columns 51 and 52, adding around 450 with three gadoliniums complexed). The Office does not appear to distinguish an antibody from a small molecule moiety. Applicants note that the molecular weight of an IgG antibody is the order of 150,000 amu (atomic mass units). As such, an IgG antibody

is thirty times larger than the largest complexes of Wedeking and three orders of magnitude larger than a folate. Given the vast size differences between a folate and an antibody, folate targeting and antibody targeting cannot simply be treated as if they are equivalent. Nothing in the combination of Wedeking et al. with Sinkule et al. teaches or suggests that the vanishingly small folate moiety (relative to an antibody) can have any useful positive effect in altering the distribution of a massive antibody or, conversely, that including an antibody in a complex, such as that of Wedeking et al., that is targeted using a folate does not interfere with targeting by that folate.

5. The reference of Sinkule et al. teaches that targeting antibodies are included in IgG-radionuclide-folate analogue conjugates for the purpose of targeting the conjugate to a desired tumor cell for uptake with a high degree of specificity which facilitates the destruction of cancerous cells while minimizing the damage to normal cells. The IgG of the disclosure encompasses the IgG antibody of the instant claims and therefore is capable of the same functions, such as not interfering with the targeting of folate and has the same properties.

6. Wedeking et al. teaches of the method of targeting the diagnostic/therapeutic agent-gadolinium-folate (folic acid) conjugate to a tumor cell expressing FBP (folate binding protein) (i.e. malignant cells).

7. Therefore, at the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the IgG antibody of Sinkule et al. for the small molecule of Wedeking et al. with the expectation of success for targeting the conjugate to a desired tumor cell for uptake with a high degree of specificity as Sinkule et al.

teaches that IgG can be successfully used to target desired tumor cells upon conjugation to a radionuclide-folate analogue species without interfering with folate targeting. Therefore, the conjugates of the combined disclosures encompass the conjugates of the instant claims and are capable of the same functions and have the same properties, such as dual binding ability.

8. Also, the antibody of the instant claims is not limited to any size (small or large) in particular.

9. Applicant asserts that the information available in the art at the time of filing would have led the skilled worker away from combining a folate with an antibody for targeting a conjugate. At page 1, lines 22-27, the specification states:

In a previous study, Shinoda et al. (1998) evaluated folate conjugated bovine serum albumin (BSA) labeled with the radionuclide indium-111, and found that there was a significant difference in pharmacokinetics and biodistribution of non-folate compared to folate labeled BSA. A high liver uptake and rapid blood clearance indicated that the folate labeled version of ^{111}In-BSA was not particularly suitable for radionuclide delivery to tumor cells expressing folate binding protein. Here, the art described in the specification indicates that adding a folate to a BSA- radionuclide complex is not particularly suitable for radionuclide delivery to tumor cells expressing folate binding protein. BSA with a mass of about 66,000 amu, like an antibody (150,000 amu for IgG), is a large protein, and Applicants submit that one skilled in the art would expect to observe similar results if a folate were added to an antibody- radionuclide complex. This teaching, is in direct contrast to the combination proposed by the Office. Applicants

submit that the favorable distribution with a folate-antibody- radionuclide complex observed in the present application is unexpected in view of the knowledge in the art at the time of filing.

10. The reference of Shinoda et al. teaches that the ***low vascular permeability of BSA*** into solid tumor tissue and inhibition of folate-mediated ^{111}In-folate-BSA uptake by tumor cells from the blood may be the rate-limiting factor of distribution (Shinoda et al. abstract). This is opposed to the reference of Sinkule et al. which teaches that targeting antibodies are included in the conjugate to target the conjugate to a desired tumor cell for uptake with a high degree of specificity, without interfering with folate targeting, while facilitating the destruction of cancerous cells and minimizing the damage to normal cells.

Conclusion

11. No claims are allowed at this time.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618